UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

6/13/00

MEMORANDUM

SUBJECT: **Phosalone.** HED Responses to Aventis CropScience Comments on the Preliminary Human Health Risk Assessment (Chemical I.D. No. 113201, DP Barcode D263987)

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Attached are the Health Effects Division (HED) responses to the 12/7/99 public comments submitted by Aventis CropScience (formerly Rhone-Poulenc Public) on the 11/1/99 Preliminary Human Health Risk Assessment on **Phosalone**. More detailed comments were prepared by Novigen Sciences, Inc. (dated 3/7/00) on behalf of Aventis to present specific arguments against the conduct of additional field trials following a meeting between Aventis and Agency representatives held 1/6/00.

Aventis Comments (paraphrased) and HED Responses

Aventis Comment 1. Aventis will submit the required product chemistry data in December, 1999. They will generate an unscheduled DNA synthesis (UDS) study. As urine samples are no longer available to permit metabolite identification for purposes of upgrading the existing rat metabolism study, Aventis will conduct a new study. Several field trials are underway and will be submitted soon. The requirement for additional

field trials will be addressed after a meeting is held with the Agency (see Comment 4 below).

HED response to Comment 1. The submitted product chemistry data concerning starting materials, formation of impurities, and UV/visible spectra have been submitted, reviewed, and found to be adequate (W. Hazel, 6/12/00, D261763 and D262645). The Agency will await receipt of the UDS and new rat metabolism studies. The field trials that were underway at the time of the 12/7/99 Aventis letter have been received, reviewed, and found to be acceptable (W. Hazel, 6/12/00, D261763 and D262645) but are not extensive enough to fulfill the requirements for residue chemistry data to support import tolerances (see comment 4 for details).

Aventis Comment 2. Aventis contends that an error has been made in the 11/1/99 Preliminary Human Health Risk Assessment in that a developmental neurotoxicity (DNT) study should not be required based on the 8/12/99 HIARC report. Also, the 9/10/99 DCI requiring such studies for the organophosphates (OPs) is claimed to state that the names of three OPs, including phosalone, have been removed from the list of active ingredients subject to the DCI.

HED response to Comment 2. Both of the Aventis arguments are true. Note, however, that the HIARC decision regarding the need for the DNT study was a weight-of-the-evidence decision. Unlike the DNT study protocol, none of the available studies was designed specifically to determine neurotoxicity in developing organisms. Also, it is the understanding of HED that the three mentioned OPs were excluded from being subject to the DCI solely because they had no U.S. registrations. HED understands that a new DCI is in preparation that will specifically require and justify a DNT study for these three OPs, including phosalone.

Aventis Comment 3. On page 6 of the 11/1/99 K. EL-Attar memorandum regarding anticipated residues (D260579), footnote 2 is incorrectly referred to as footnote 1 on the bottom of the page; the text is correct.

HED response to Comment 3. Aventis is correct regarding the error.

Aventis Comment 4. Following a 1/6/00 meeting between Aventis and Agency representatives, Novigen Sciences, Inc. (dated 3/7/00), on behalf of Aventis, submitted specific arguments against the conduct of field trials in addition to the nearly complete Canadian field trials (two on apples and five on cherries). These arguments include:

> **(a) Grapes.** Three Italian field trials are available. The principal countries having phosalone registrations are Italy, France, Spain, Portugal, and Canada. The Major commodities imported by the U.S. from these countries are juice and wine. A metabolism study demonstrates that phosalone residues don't concentrate in juice (1.4% of the TRR). Therefore, one wouldn't expect

detectable residues in wine. Of 107 FDA samples of grapes (fresh, juice and wine) monitored during the 1992-98 period from countries having phosalone registrations, none bore detectable residues.

(b) Pome fruit. As per the Import Tolerance Guidelines, 12 studies would be required for **apples**. Fifteen European field trials are available. Because about 5% of imported apples are imported from Canada, two new Canadian trials have been submitted. Residues from Canadian trials (0.75-1.95 ppm) are within the range of the European trials (0.38-1.5 ppm). Canadian studies reflected three applications of the 500 g/L SC at 1.5 kg/ha with a 30-day PHI. European studies involved three applications of an EC or the 30% WP at 0.6 kg/ha with a 14-day or 21-day PHI in France and Italy, respectively. Of 88 apple samples from countries with phosalone registrations FDA analyzed from 1992-98, five bore detectable residues the highest of which was 0.2 ppm. In the case of **pears**, three trials would be required and four are available. Canadian trials are unnecessary because only 0.14% of imported pears come from Canada and less than 0.1% of the available market in the U.S. are imported from countries having phosalone registrations. Of 86 FDA import samples, all bore nondetectable residues. **Overall**, no additional field trials are needed for phosalone residues on pome fruit.

(c) Stone fruit. As per the Import Tolerance Guidelines, three trials are required for peaches, plums, and cherries. Seven **cherry** trials are available from Europe. Because >5% of imported cherries come from Canada, five new Canadian trials were conducted; EPA's requirement has been met. Of **peaches** available in the U.S., 0.05% are imported from countries having phosalone registrations. Four European trials are available. Of 59 FDA samples from countries having phosalone registrations, only one bore detectable residues (0.13 ppm). No additional peach trials should be required. Regarding **plums**, neither field trial nor monitoring data are available. Residues in cherries treated twice at 0.6 kg/ha with a PHI of 14-17 days are similar to residues in peaches treated three times at 0.9 kg/ha with a PHI of 18-26 days. "Residue data on plums following the treatment regimen of peaches typically results in comparable residues." **In summary**, no additional stone fruit trials should be required. Note that JMPR set a Codex MRL of 2 mg/kg in stone fruit based on cherry and peach data.

HED response to Comment 4.

(a) Grapes. Three Italian trials are available from two locations. Only two of these trials involved two treatments. The treatment rate was 0.6 kg/ha with a 21-day PHI (proposed European GAP) which is much less than the Canadian GAP. Only one formulation class was tested (a 232 g/L EC) whereas the Import Tolerance Guidelines require that every formulation class be tested. The retreatment interval was 82 days which is likely to be much longer than the common commercial practice thus reducing the opportunity for residues to accumulate. No trials were conducted at the Canadian GAP, i.e., three

applications per season at 1 kg/ha with a 21-day PHI. Also, no trials were conducted at the French GAP, i.e., an unspecified number of applications per season at 1 kg/ha with a 14-day PHI. HED has reservations about using juice from a grape metabolism study to determine the potential for residue concentration in white wine although it is adequate for white grape juice. However, it is not appropriate to use a grape metabolism study to determine the potential for residue concentration in **red** wine because the skins of red grapes are typically present during fermentation. HED must have representative field trial data to determine the appropriate raisin tolerance. Grape trials are needed that reflect the Canadian GAP because there is great potential for residues to be higher than those resulting from the lower application rates in other countries. Because the grape use is apparently going to be deleted from French labels, we have decided that **studies need be conducted only in Canada at their GAP but that both the EC and either the WP or FlC should be applied in side-by-side studies in two major grape growing regions; the retreatment intervals tested should reflect common commercial practice.**

(b) Pome fruit. Aventis acknowledges that apple studies are required from Canada because it is a major exporter to the U.S. However, only two studies were conducted (at the Canadian GAP); these two studies partially satisfy the requirements for an import tolerance. As important as apples are to the U.S. diet, we feel that it is important to have one additional trial conducted in Canada in one major grape growing region. The GAP should be followed to include common commercial retreatment intervals. Side-by-side studies involving application of the EC and either the WP or FlC are necessary. HED has decided not to require pear field trials due to the very low percent of imported pears available for consumption. However, a pome fruit crop group tolerance may not be established without the additional two pear field trials conducted at the Canadian GAP.

(c) Stone fruit. The new Canadian **cherry** field trials tentatively satisfy the requirements to support an import tolerance; if the side-by-side studies to be conducted on other crops indicate differences between residues resulting from different formulation classes, additional trials will be required testing the EC formulation. The four-fold higher residues on some tart cherries following treatment at the Canadian GAP support the need for additional testing of other commodities. In the case of **peaches and plums**, HED agrees that the percentage of available fruit from countries having phosalone registrations is very low. However, we do not feel that cherry data may be translated to these other stone fruits because of fruit size differences and because peaches have a hairy surface. Also, we need representative plum field trial data to determine the proper tolerance level in dried prunes. HED has decided to reduce the number of trials to be conducted on peaches and plums from three to two each but to require side-by-side trials testing the EC and either the FlC or WP. Trials should reflect the Canadian GAP.

General Issue. Note that tolerances will be reassessed periodically, at least every 5 years for phosalone as per FQPA because anticipated residue data were used to calculate dietary risk. At the same time tolerances are reassessed, the Agency is likely to perform an updated determination of the percent crop imported to the U.S. from various countries.

cc: F. Fort (HED), J. Dawson (HED), W. Hazel (HED), L. Mendez (HED), D. Anderson (HED), D. Young (EFED), List A File, SF, RF
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